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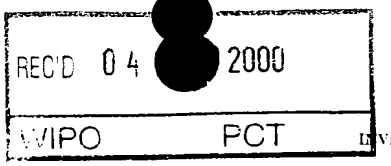

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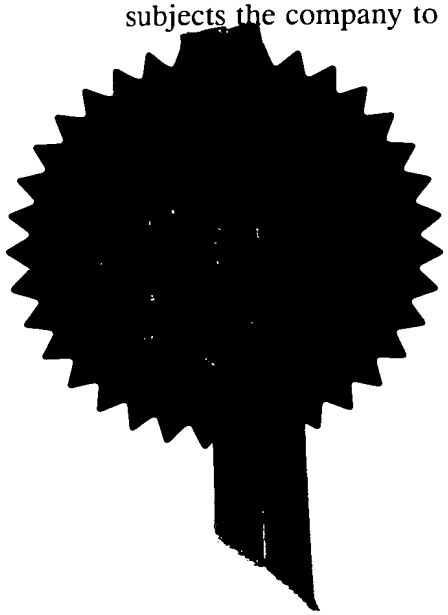

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Title of invention

Pharmaceutical Formulation

Applicant's details

First or only applicant

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Corporate Name

SmithKline Beecham p.l.c.

Country (*and State of incorporation, if appropriate* United Kingdom

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Agent's name: Ralph Francis Walker

Agent's address: SmithKline Beecham
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New Horizons Court (2NHC/1)
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Agent's ADP number:

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5. Are you claiming that this application be treated as having been filed on the date f filing of an earlier applicationYes

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Inventorship

- any a :ant is not an inventor
- there is an inventor who is not
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7. Are you (the applicant or applicants) the sole inventor or the joint inventors?
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Please supply duplicates of claim(s), abstract, description and drawings).

Checklist

8a Please fill in the number of sheets for each of the following types of document contained in this application

Claims 6 Specification 17

Abstract Drawing(s) 3 only

8b Which of the following documents also accompanies the application?

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Patents Form 9/77 - Preliminary Examination Report -

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Pharmaceutical Formulation

This invention relates to pharmaceutical formulations, being a dosage form comprising two or more connected sub-units, particularly for oral dosing.

Various types of pharmaceutical dosage form are known for oral dosing. Pharmaceutical capsules are well known, generally being intended for oral dosing. Such capsules generally comprise an envelope wall of a pharmaceutically acceptable, e.g. orally injestible, polymer material such as gelatin, although other materials for capsule walls, e.g. starch and cellulose based polymers are also known. Such capsules generally have soft walls made by making a film on a capsule former, which is then allowed to dry. Rigid walled capsules made by injection moulding are also known, see for example US 4576284, US 4591475, US 4655840, US 4738724, US 4738817 and US 4790881 (all to Warner Lambert). These disclose specific constructions of capsules made of gelatin, starch and other polymers, and methods of making them by injection moulding of hydrophilic polymer - water mixtures. US 4576284 specifically discloses such capsules provided with a cap which closes the capsule, and which is formed in situ on the filled capsule by moulding. US 4738724 discloses a wide range of rigid capsule shapes and parts.

Multi-compartment capsules, including those of the type where each compartment has different drug release characteristics or for example contains a different drug substance or formulation are also known, for example in US 4738724 (Warner-Lambert), US 5672359 (University of Kentucky), US 5443461 (Alza Corp.),WO 9516438 (Cortecs Ltd.), WO 9012567 (Helminthology Inst.), DE-A-3727894, BE 900950 (Warner Lambert), FR 2524311, NL 7610038 (Tapanhony NV), FR 28646 (Pluripharm), US 3228789 (Glassman), US 3186910 (Glassman) among others.

Pharmaceutical dosage forms are also known which comprise a matrix of a solid polymer, in which a drug substance is dispersed, embedded or dissolved as a solid solution. Such matrixes may be formed by an injection moulding process. This technology is discussed in Cuff G, and Raouf F, Pharmaceutical Technology June 1998 p 96-106. Some specific formulations for such dosage forms are for example disclosed in US 4,678,516; US 4,806,337; US 4,764,378; US 5,004,601; US 5,135,752; US 5,244,668; US 5,139,790; US 5,082,655 among others; in

which a polyethylene glycol ("PEG") matrix is used and solid dosage forms are made by injection moulding.

The content of the above-mentioned background publications is incorporated herein by way of reference.

It is an object of this invention to provide an alternative and for some applications improved pharmaceutical dosage form which provides inter alia greater flexibility in producing a dosage form adapted to a patient's specific administration requirement. Other objects and advantages of the invention will be apparent from the following description.

According to this invention a pharmaceutical oral dosage form is provided, which comprises a plurality of drug-containing sub-units connected together in the assembled dosage form and being retained together by the connection at least prior to administration to a patient, at least one of the sub-units being a solid sub-unit comprising a solid matrix of a polymer which contains a drug substance, the polymer being soluble, dispersible or disintegrable in the patient's gastro-intestinal environment to thereby release the drug substance.

Suitably adjacent sub-units may be connected together in the assembled dosage form and retained together by the connection at least prior to administration to a patient.

In one embodiment all of the sub-units in the dosage form of this invention may be solid sub-units, e.g. two or more such solid sub-units, e.g. three such solid sub-units.

In an alternative and preferred embodiment of this invention, one or more of the sub-units comprise a solid sub-unit as described above, and one or more of the other sub-units comprises a capsule compartment bounded by a wall made of a pharmaceutically acceptable polymer material, one or more of the said capsule compartments containing a drug substance.

Each of a plurality of solid sub-units may comprise the same polymer and/or drug substance, or alternatively may comprise different polymers and/or drug substances. Suitably each of such two or more solid sub-units may contain the same drug substance but releasable in the gastro-intestinal tract of the patient at different rates, at different times after administration to the patient or at different places in

the patient's gastro-intestinal system. Alternatively each of such two or more solid sub-units may contain a different drug substance, each of which may be released at the same or a different rate or time after administration or place in the patient's gastro-intestinal system.

The connectable nature of these sub-units advantageously enables various sub-units having different drug release characteristics and/or contents to be assembled and connected together to produce a dosage form. In a preferred form the sub-units have common interconnectable parts so that the sub-units of the invention may be assembled in various combinations using the same basic units of solid sub-units or of solid sub-units and capsule compartments.

The invention also provides individual sub-units adapted for use in the assembled dosage form.

Suitably in the assembled dosage form there are at at least two, for example especially three or more, e.g four sub units. Such an assembled dosage form may comprise three or four sub-units comprising one, two or three solid sub-units, combined with one, two or three capsule sub-units. Three or more such sub-units may for example be linearly disposed in the assembled dosage form, e.g. in an arrangement comprising two end sub-units at opposite ends of the line, and one or more intermediate sub-units. For example such an assembled dosage form may comprise a solid sub-unit connected to a capsule compartment; a solid sub-unit between two end capsule compartments; an end capsule compartment, an intermediate capsule compartment and an end solid sub-unit; an end capsule compartment, an intermediate solid sub-unit and an end solid sub-unit; or an intermediate capsule compartment between two end solid sub-units. An assembled dosage of four such sub-units may comprise two end solid sub-units, an intermediate solid sub-unit and an intermediate capsule compartment. Alternately it may comprise two end solid sub-units with two intermediate capsule sub-units, or other combinations of sub-units.

In the assembled dosage form the adjacent sub-units may be connected together by any suitable means. Preferably the adjacent sub-units are connected together by means of a weld, e.g. a thermal weld at the area where two adjacent sub-units are in contact, an ultrasonic or inductive weld, adhesive (e.g. curable

adhesives such as UV curable adhesive). This weld may be achieved by bringing sub-units into adjacent contact and applying localised heating or an ultrasonic horn (suitable types are commercially available and will be apparent to those skilled in the art) or the adhesive to the region of contact.

Adjacent sub-units may have substantially planar regions of their surface which may be brought into contact and then the weld may be formed, or may have regions of their surface of complementary shapes, thereby facilitating connecting sub-units together.

Preferably, additionally or alternatively adjacent sub-units may be provided with respectively inter-connectable first and second connectable parts such that the first part on one sub-unit may connect with the second part on an adjacent sub-unit in a suitable configuration, e.g. into the above-mentioned linear configuration. The connectable parts may be such as to facilitate the assembly together of the sub-units in preferred configurations, e.g. the connectable part(s) on one sub-unit may be such as to only connect with a corresponding part on other selected sub-units but not with non-corresponding connectable parts on other sub-units. Alternatively the connectable parts on the sub-units may be common so that the sub-units may be connected together in a wide range of combinations. This means inter alia that otherwise different capsule compartments or solid sub-units have mutually connectable parts so that the different capsule compartments or solid sub-units may be connected together in different combinations of solid sub-units or solid sub-units and capsule compartments The connectable parts may also be such that the connection between the first and second connectable parts on adjacent sub-units contributes to the retention of the adjacent sub-units together, e.g. via a retaining friction, snap, screw or other kind of fit between the connectable parts.

For example in one embodiment the respective first and second connectable parts may be respectively interlocking parts. For example the first or second part may be a female socket part, and the corresponding second or first connecting part may be a corresponding male part which fits into the female socket with a retaining friction, snap, screw or other kind of interlocking fit. If for example these male and female parts are common then any male part on any solid sub-unit or capsule

compartment may interconnect with any female part on another solid sub-unit or capsule compartment.

In a friction fit for example the male part may be slightly larger than the female socket such that force needs to be applied against the natural resilience and contact friction of the male and female parts to cause the male part to enter the female socket, and similar force needs to be applied to separate them. In a snap fit for example the male and female parts may be provided with a concavity and a corresponding convexity, such as a ridge and groove, which lock together as the parts are forced together against the natural resilience of the parts. Such a ridge and groove may for example comprise a co-operating circumferential or part circumferential bead and groove, for example located about the circumference of a connectable male and female part.

Above-mentioned US 4576284 and US 4738724 for example, the contents of which are included herein in their entirety by way of reference, disclose a range of interlocking parts of this general type by means of which capsule compartments may be made to interlock together. See for example Figs. 1, 2 and 3 of US 4576284 which discloses interlocking parts by means of which a cap may be retained on the mouth of a capsule, and Figs. 4 – 43 of US 4738724 which disclose numerous interlocking parts by means of which part capsule shells may interlock and be retained together as an assembled complete capsule.

For example in a dosage form of the invention comprising a linear disposition of three or more e.g. four, sub-units, the or each intermediate sub-unit(s) may be provided with one or more connectable parts, which may connect with one or more connectable parts on an adjacent intermediate sub-unit. Also the end sub-unit(s) may be provided with one or more connectable parts which may connect with connectable parts on an adjacent intermediate sub-unit and/or with one or more connectable parts on another end sub-unit. By means of this two end sub-units may connect together in a dosage form comprising two sub-units, or two end sub-units may be connected to one or more intermediate sub-units. By using common first and second connectable parts on the sub-units the various end and intermediate sub-units may be made such that they may be connected together in various combinations of assembled dosage forms.

In one embodiment one or more, e.g. all, of the sub-units may for example be substantially cylindrical, which term includes shapes which have a circular, oval or oblate circular cross section across the longitudinal axis. Solid sub-units may also be substantially cylindrical in shape. Such substantially cylindrical sub-units may be provided with connectable parts at one or both of their longitudinally disposed ends so that the assembled dosage form may also be overall of a substantially cylindrical shape.

Sub-units which are capsule compartments may for example be substantially tub-shaped, i.e. having a base closed by a base wall, and side walls extending upward from the base wall, and an upper open mouth. With such a construction capsule compartments may connect together by the base of a first compartment fitting into the open mouth of an adjacent capsule compartment, so as to close the mouth of the adjacent capsule compartment, and such that the base wall of the first compartment physically separates the compartments.

Solid sub-units may for example be shaped so as to fit as a plug into or a cap over the open mouth of an adjacent capsule compartment so as to function as a closure for the mouth. Alternatively solid sub-units may be shaped so as to fit adjacent to and connect with the outer surface of the base wall of a capsule compartment. For example the base of such a tub-shaped capsule compartment may be provided externally with a male or female part and an adjacent solid sub-unit may be provided externally with a corresponding interconnecting female or male part. Capsule compartments may be formed with a base part that can connect with the mouth opening of an adjacent capsule compartment so as to function as a closure for the mouth in the above-described manner.

For example in the above described tub-shaped capsule compartments the base part of the first capsule compartment may comprise a male part and the mouth opening of the second compartment may comprise a corresponding female socket. The base part of the first compartment may be shaped to fit in this way into the mouth opening of the second compartment or to engage with a solid sub-unit A weld between the sub-units may then be formed in the region of contact e.g. between the base of the first compartment or a solid sub-unit, and the mouth of the second compartment. Additionally or alternatively for example the sub-units may

be provided with connectable parts to enable a retaining friction, snap, screw or other kind of interlocking fit.

In such an assembly, a capsule compartment may have its mouth opening closed by the base wall of an adjacent compartment or by part of a solid sub-unit fitting into its open mouth in the manner of a plug closure, or over its mouth opening in the manner of a cap closure. Alternatively a capsule end compartment can be provided with some other type of closure for its mouth opening, particularly if it is connected by its base to an adjacent sub-unit. The closure may for example be made from the same, or a different, polymer than the polymer material of the compartment. This closure may for example comprise an over-cap for example fitting around the outer surface of the side walls of the compartment, as in the general manner disclosed in US 4196565 or US 4250097 or alternatively the closure may comprise a plug type of closure. Above-mentioned US 4576284 discloses some suitable types of closure for capsule compartments which are suitable for use with the present invention. The closure may be retained in place on the mouth opening of its compartment by a wall e.g. as described above, or additionally or alternatively the closure and mouth opening may be provided with features to enable a retaining friction, snap, screw or other kind of interlocking fit.

Adjacent solid sub-units may for example have respective connectable male and female parts which can interlock to connect such adjacent parts together in the assembled dosage form.

Alternative ways of assembling the sub-units are encompassed within the scope of the invention.

For example rather than having an open mouth which is closed by the presence of an adjacent compartment, one or more capsule compartments may be made closed and for example containing the drug substance, and may in this closed form connect in the manner described above with the one or more adjacent sub-units.

For example one or more capsule compartments may be made in the form of two part compartment shells, each part compartment shell comprising a closed end and side walls and having a mouth opening opposite the closed end, which connect together, e.g. by the means discussed above, with their mouth openings facing, to

form the capsule compartment. One or both of the closed ends may connect with an adjacent sub-unit, which may be a solid sub-unit or a capsule compartment, e.g. by the means discussed above. For example if the dosage form comprises a linear assembly of sub-units one or both closed ends of an intermediate capsule compartment(s) may be connectable to an end sub-unit. For example each end sub-unit may be a substantially tub-shaped capsule compartment as described above and may have a mouth opening that is connectable to the closed end in the manner described above, or may be a solid sub-unit.

The wall of capsule compartments and the matrix of solid sub-units may comprise of any pharmaceutically acceptable polymer which is capable of being formed, e.g. by an injection moulding process, into the required shape. Suitable polymer materials include: polyvinyl alcohol (PVA), natural polymers (such as polysaccharides like pullulan, carrageenan, xanthan or agar gums), polyethylene glycols (PEG), polyethylene oxides (PEO), mixtures of PEGs and PEOs, hydroxypropylmethylcellulose (HPMC), methylcellulose, hydroxyethylcellulose, hydroxyethyl methylcellulose, hydroxypropylcellulose, methacrylic acid copolymer (such as Eudragit E™, Eudragit L™ and/or Eudragit S™), ammonium methacrylate copolymers (such as Eudragit RL™ and/or Eudragit RS™), carboxymethylcellulose, povidone (polyvinyl pyrrolidone), polyglycolysed glycerides (such as Gelucire 44/14™, Gelucire 50/02™, Gelucire 50/13™ and Gelucire 53/10™), carboxyvinyl polymers (such as Carbopols™), polyoxyethylene-polyoxypropylene copolymers (such as Poloxamer 188™).

It is also known to form solid bodies suitable for the solid sub-units of this invention using processes of powder compression. For such processes amylose, cross-linked amylose and amylose-pectin combinations may be suitable.

Preferred polymers are orally injestible polymers and include polyvinyl alcohol, hydroxypropyl methyl cellulose, and other cellulose-based polymers. Preferred polymers also include polymer materials which preferentially dissolve or disintegrate at different points in the digestive tract. Such polymers include the well-known Eudragit™ series of commercially available polymers. Examples of these include Eudragit E™, such as Eudragit E 100™, which preferentially dissolves in the more acid pH of the stomach, or enteric polymers such as Eudragit L™ and/or

Eudragit S™ which preferentially dissolve in the more alkaline pH of the intestine, and Preferred polymers also include polymers which dissolve slowly, e.g. a predetermined rate in the digestive tract, such as Eudragit RL™, e.g. Eudragit RL 100™, and/or Eudragit RS™ e.g. Eudragit R100™, and/or blends of such Eudragit™ polymers.

The polymer material(s) may include other substances to modify their properties and to adapt them to various applications, including for example the following general classes of substances. Surfactants, such as Polysorbate 80™, sodium lauryl sulphate, and Polyoxyl 40™ hydrogenated castor oil. Absorption enhancers, such as Labrasol™, Transcutol™; glidants, such as talc, magnesium stearate, silicon dioxide, amorphous silicic acid, fumed silica, Simeticone™; plasticizers, such as triethyl citrate, acetyl triethyl citrate, tributyl citrate, acetyl tributyl citrate, glyceryl monostearate, diethyl phthalate, dibutyl phthalate, propylene glycol, triacetin and castor oil; substances for release modification, such as ethyl cellulose and cellulose acetate phthalate; disintegrants, such as sodium starch glycollate, croscarmellose sodium, crospovidone (cross-linked polyvinyl pyrrolodone), colouring agents, flavouring agents and sweetening agents.

The sub-units may additionally be provided with constructional features and/or include materials in the polymer materials of which they are made to enhance the ease with which they can be welded together.

The dimensions and shape of each of the sub-units and hence of the overall assembled dosage form may be determined by the nature and quantity of the material to be contained therein and the intended mode of administration and intended recipients. For example a dosage form intended for oral administration may be of a shape and size similar to that of known capsules intended for oral administration.

The dosage form of this invention enables the assembly together of sub-units which differ in their drug content and/or drug content release characteristics to provide a dosage form tailored to specific administration requirements.

For example two or more sub-units may each contain different drug substances, and/or different drug substance formulations, and/or the same drug in

different formulations, so that a combination of two or more drug substances or formulations may be administered to a patient.

The dosage form is particularly suitable for presentation as an oral dosage form containing one or more drug substances suitable for oral administration.

The dosage form is suitable for all types of drug substance. As explained in Cuff G. and Raouf F. (op.cit.), in the matrix of solid sub-units the drug substance may be present in various states. For example it may comprise discrete particles dispersed in the matrix, for example in the case of particles that do not readily dissolve in the fluid polymer. Alternatively the drug substance may be present as a solid solution in the solid polymer of the matrix. Alternatively some of the drug substance may comprise discrete particles and some may be present as a solid solution in the polymer. When two or more solid sub-units are present the drug substance present in each solid sub-unit may be in the same or in different states, e.g. having different drug substance release characteristics.

The drug substance(s) contained in any capsule compartment may be present in any suitable, e.g. conventional, form, e.g. as a powder, granules, compact, microcapsules, gel syrup or liquid provided that the capsule compartment wall material is inert to the liquid content of the latter three forms. The contents of the compartments, e.g. drug substances, may be introduced into the compartments by standard methods such as those used conventionally for filling capsules, such as dosating pins or die filling.

The sub-units may differ from each other in their drug content release characteristics, and this may be achieved in various ways.

For example one or more solid sub-units and/or capsule compartments may be substantially immediate release, i.e. releasing their drug content substantially immediately upon injestion or on reaching the stomach. This may for example be achieved by means of the matrix polymer or the capsule compartment wall dissolving, disintegrating or otherwise being breached to release the drug content substantially immediately. Generally, immediate-release sub-units are preferably provided by being capsule compartments.

For example one or more solid sub-units and/or capsule compartments may be sustained-release sub-units. Preferably these are solid sub-units, as a bulk matrix

of polymer is likely to dissolve or disperse more slowly to release its drug content that a thin walled capsule.

For example one or more solid sub-units and/or capsule compartments may be pulsed-release sub-units for example releasing their drug content at a specific predetermined point in a patients gastro-intestinal system. This may be achieved by the use of polymer materials which dissolve or disperse only at defined pH environments, such as the above mentioned Eudragit polymers.

In the case of the above-described linear arrangement of sub-units, suitably one of the end sub-units, particularly a capsule compartment may be a substantially immediate-release compartment, so that the disruption of this end sub-unit has little or no influence on the other sub-units, e.g. the other end sub-unit or the intermediate sub-unit(s), in the assembly. In such a case the other end and the intermediate sub-unit(s) may be delayed release compartments, i.e. releasing their drug content at a delayed time after administration. For example in the case of oral administration these delayed release sub-units may release their drug content in the stomach, small or large intestine.

Determination of the time or location within the gastro-intestinal tract at which a sub-unit releases its drug substance content may be achieved by for example the nature of the sub-unit material, e.g. a solid sub-unit matrix polymer or a capsule compartment wall material, or in the case of an end compartment closed by a closure the nature of the closure material. For example the wall of different, e.g. adjacent, compartments may be made of polymers which are different or which otherwise differ in their dissolution or disintegration characteristics so as to endow different compartments with different drug release characteristics. Similarly for example the polymer matrix material of different, e.g. adjacent, sold sub-units may be made of polymers which are different or which otherwise differ in their dissolution or disintegration characteristics so as to endow different solid sub-units with different drug release characteristics.

For example the matrix, wall or closure material may be a polymer which dissolves or disperses at stomach pH to release the drug substance in the stomach. Alternatively the wall material of different compartments may differ so that different compartments have different release characteristics.

For example a solid sub-unit or a capsule compartment may have respectively a matrix or a wall or a closure comprising an enteric polymer which dissolves or disperses at the pH of the small or large intestine to release the drug substance in the intestine. Suitable such polymers have been described above.

Additionally or alternatively the wall material may differ in thickness between compartments so that thicker walled compartments disrupt more slowly than thinner walled compartments.

Additionally or alternatively the compartment walls or the closure may have areas or points of weakness which preferentially dissolve and determine the time of onset and/or rate of release of the drug substance content. For example such points of weakness may comprise holes, e.g. small holes, e.g. laser-drilled holes in the compartment wall or the closure, these holes being closed and/or covered with a film of a polymer material that dissolves at a pre-determined point in the digestive tract, for example an enteric polymer material.

The sub-units may additionally or alternatively have surface or other constructional features which modify their drug release characteristics. For example solid sub-units may be provided with internal cavities or channels to create a large surface area. For example solid sub-units may be in the form of hollow cylinders, donuts, or toroids, which shapes are known to tend towards first-order dissolution or erosion in liquid media and correspondingly to tend toward first-order release of drug content dispersed therein.

The sub-units may for example be made from such polymer materials using conventional injection moulding processes, i.e. in which a fluid polymer is injected under pressure into a precisely made die cavity in a mould block. Injection moulding processes can enable the sub-units to be made with the precision necessary to achieve connection by tight friction-fit or snap-fit interlocking. Suitable techniques of injection moulding are known from for example the art of manufacture of small plastic components e.g. small parts of LEGO™ toys. Processes such as those described in Cuff. G and Raouf. F (op. cit) may be used to manufacture such solid sub-units and capsule compartments via injection moulding. The Eudragit ™ polymers discussed above for example are extrudable and may for example be plasticised with e.g. triethyl citrate, or glyceryl monostearate.

Consequently the invention also provides a moulding process, for example an injection moulding or powder compression process, wherein sub-units, including the solid sub-units and capsule compartments of the dosage form are made in respective mould cavities. The invention also provides a mould or die, for example an injection mould or powder compression mould or die suitable for use in this moulding process. Such a mould or die may have a mould cavity corresponding to the shape of the sub-unit.

The invention will now be described by way of example only with reference to:

Fig.1 which shows a longitudinal sectional view of a dosage form of the invention assembled together.

Fig. 2 which shows a longitudinal sectional view of another dosage form of the invention assembled together.

Fig. 3 which shows a longitudinal sectional view of another dosage form of the invention assembled together.

Referring to Fig. 1, a dosage form 11 is shown comprising three sub-units 12, 13, 14 linearly disposed in the assembled dosage form, in an arrangement comprising two end compartments 12, 14 at opposite ends of the line, and one intermediate solid sub-unit 13. The compartments 12 and 14 and the solid sub-unit 13 are substantially cylindrical. The compartments 12 and 14 are substantially tub-shaped, i.e. each having a base closed by a base wall 12A, 14A, and each having side walls 2B, 4B extending upward from the base wall 12A, 14A, and an upper open mouth. Each of the compartments 12 and 14 is made of polyvinyl alcohol polymer by injection moulding.

The solid sub-unit 13 is also substantially cylindrical, and has its base end 13A formed into a male plug shape capable of engaging with and thereby closing the open mouth of either compartment 12 or 14. As shown in Fig. 1 the base end 13A of solid sub-unit 13 fits into and is in engagement with the mouth opening of compartment 14. The upper end of solid sub-unit 13 has its upper end 13B formed into a female socket connector capable of engaging with the shape of the base 12A or 14A of capsule compartment 12 or 14, as shown in Fig. 1 being in engagement with the base of compartment 12.

The compartments 12, 14 and solid sub-unit 13 connect together by the base 12A of compartment 12 fitting into the upper socket 13B of adjacent solid sub-unit 13, and the base 12A of the solid sub-unit 13, fitting into the open mouth of adjacent compartment 14 so as to close its mouth. In this assembly of sub-units 12, 13, 14 the base part of an upper sub-unit 12, 13 comprises a male part and the mouth opening or upper socket of a lower sub-unit respectively 13, 14 comprises a female socket.

Compartment 14 is an end compartment 13 and has its mouth opening closed by the base end 13A of solid sub-unit 13. The other upper end compartment 12 is closed by a closure 15 having a plug part 16 which is dimensioned to fit into the mouth opening of the compartment 12.

The base parts 12A and 13A and the plug part 16, fit into the respective mouth openings of the compartments 12 and 14. A thermal weld is formed between the base parts 12A and 13A, the plug part 16, and the respective mouth openings and upper socket of the compartments 12, 14 and the solid sub-unit 13 at the region where these parts are in contact. Each of the base parts 12A, 13A, and the plug part 16, and the corresponding respective mouth openings and upper socket of the compartments 12, 13 and 14 may additionally or alternatively be provided with features (not shown) such as a convex circumferential bead and a corresponding circumferential groove into which the bead may fit, such that the base part 12A, 13A, the mouth openings of the compartments 12 and 14, the upper socket 13B and the plug part 16 and mouth opening of compartment 12 may connect together by a snap fit interlocking engagement overcoming the natural resilience of the polymer material of the base part and mouth opening.

The base parts 12A, 13A, 14A of the compartments 12, 13, 14, the mouth openings of the compartments 12 and 14, the upper socket 3B and the plug part 16 are all of common dimensions so that the compartments 12 and 14 and the solid sub-unit may be fitted together in other linear combinations, and so that the plug 15 may be used to close the mouth opening of the other compartments 14.

Similarly, two or more than the three sub-units 12, 13 or 14, may be connected together in an analogous manner to that shown in Fig 1.

Fig. 2 shows another dosage form assembly 21. This assembly 21 also comprises three sub-units 22, 23, 24 in a linear assembly of an end compartment 22, an intermediate compartment 23 and an end solid sub-unit 24. The intermediate compartment 23 is made in the form of part compartment shells 23A and 23B, each part shell 23A, 23B comprising a closed end 23C and 23D and side walls 23E and 23F with a mouth opening opposite each closed end 23C and 23D. The mouth openings of the two part shells 23A and 23B are each provided respectively with a male connectable part 25 and a female connectable part 26. These part shells 23A, 23B connect together with their respective male and female parts 25 and 26 connecting to form the capsule compartment 23. Both of the closed ends 23C, 23D are externally provided with connectable parts 27, 28.

The end compartment 22 is in the form of a tub-shaped compartment and has a mouth opening 29, which comprises a female part that corresponds in shape with connectable part 27 on the intermediate compartment 23 to connect the assembly 21 together.

The end solid sub-unit 24 is formed as a substantially cylindrical body, having a connectable part 210 in the form of a female socket engageable with either of the connectable parts 27 or 28 on intermediate capsule compartment 23. As shown in Fig. 2 the connectable part 210 on solid sub-unit 24 is connected to the part 28 on capsule compartment 23.

As with the dosage form of Fig. 1, a thermal weld is formed between the parts 25, 26, 27, 29, 28 and 210 at the region where these parts are in contact. Each of these parts 25, 26, 27, 29, 28 and 210 may additionally or alternatively be provided with features (not shown) such as respectively a convex circumferential bead and a circumferential groove into which the bead may fit, such that these interlocking parts may connect together by a snap fit engagement.

Fig. 3 shows another dosage form assembly 31. This assembly 31 comprises four sub-units 32, 33, 34, 35 in a linear assembly of an end solid sub-unit 32, an intermediate solid sub-unit 33, an intermediate capsule compartment 34 and an end solid sub-unit 35. The intermediate capsule compartment sub-unit 34 has a mouth opening 36, and the immediately adjacent rim 37 of this mouth opening 36 is formed as a male connectable part. The end solid sub-unit 35 is substantially

hemispherical and is formed as a closure cap for the tub-shaped intermediate capsule compartment 34, being formed at its lower end as a female connectable part 38 which fits in a sealing engagement with the part 37. The closed lower end 34A of compartment 34 is externally provided with a female connectable part 39.

The intermediate solid sub-unit 33 has its upper end formed as a male connectable part 310 engageable with the part 39 of the compartment 34, and a lower end formed as a female connectable part 311.

The end solid sub-unit 32 is in the form of a rounded bottomed cylinder having a male connectable part 312 part that corresponds in shape with connectable part 311 on the intermediate compartment 33. Each of these parts 37, 38, 39, 310, 311, 312 may additionally or alternatively be provided with features (not shown) such as respectively a convex circumferential bead and a circumferential groove into which the bead may fit, such that these interlocking parts may connect together by a snap fit engagement.

Designated 313 is an alternative construction of the intermediate solid sub-unit 33, parts common with the sub-unit 33 being numbered correspondingly. The sub-unit 313 has an internal cylindrical bore 314 so that the sub-unit 313 is of a generally hollow cylindrical shape. The bore 314 may alternatively be of a longitudinally tapering e.g. generally cylindrical shape.

By connection of the various connectable parts 37, 38, 39, 310, 311, 312 the assembly 31 may be connected together along the axis shown.

Each of the compartments and sub-units 12, 13, 14, 22, 23, 24, 32, 33, 34, 35 in Figs. 1, 2 and 3 may be made of the same or different polymer and may have the same or different drug release characteristics. The intermediate compartments 23, 34 are more suitable for a modified release compartment, as dissolution or disruption of the end compartments 12, 14 and 22 before the intermediate compartments 23 and 24 can occur without disturbance of these intermediate compartments.

The solid sub-units 13, 24, 32, 33, 36 and 313 are more suitable as a sustained release sub-unit, as the dissolution of the matrix polymer is likely to occur more slowly than the disruption of the thin wall of a capsule compartment. The

hollow bore 314 of unit 313 gives the solid unit 313 a dissolution rate tending toward first-order dissolution kinetics.

Each of the sub-units 12, 13, 14, 22, 23, 24, 32, 33, 34, 35 may contain the same or different drug substance and/or formulation. This may for example be in the form of powder, granulates, or other solid forms. Alternatively the capsule compartments 12, 14, 22, 34 may contain liquid, gel etc. formulations (not shown). The end sub-unit 35 may contain a drug substance or alternately may simply comprise a solid polymer cap devoid of drug substance.

Claims:

1. A pharmaceutical oral dosage form, which comprises a plurality of drug-containing sub-units connected together in the assembled dosage form and being retained together by the connection at least prior to administration to a patient, at least one of the sub-units being a solid sub-unit comprising a solid matrix of a polymer which contains a drug substance, the polymer being soluble, dispersible or disintegrable in the patient's gastro-intestinal environment to thereby release the drug substance.

2. A dosage form according to claim 1 wherein all of the sub-units are solid sub-units.

3. A dosage form according to claim 1 wherein one or more of the sub-units comprises a solid sub-unit and one or more of the other sub-units comprises a capsule compartment bounded by a wall made of a pharmaceutically acceptable polymer material, one or more of the said capsule compartments containing a drug substance.

4. A dosage form according to any preceding claim, wherein the sub-units have common interconnectable parts so that the sub-units of the invention may be assembled in various combinations using the same basic units of solid sub-units or of solid sub-units and capsule compartments.

5. A dosage form according to any preceding claim having three or more sub units.

6. A dosage form according to claim 5 comprising three or four sub-units comprising one, two or three solid sub-units, combined with one, two or three capsule sub-units.

7. A dosage form according to claim 5 or 6 in which three or more sub-units are linearly disposed in the assembled dosage form in an arrangement comprising two end sub-units at opposite ends of the line, and one or more intermediate sub-units.

8. A dosage form according to any one of claims 3 to 7 comprising a solid sub-unit connected to a capsule compartment; a solid sub-unit between two end capsule compartments; an end capsule compartments, an intermediate compartment compartment and an end solid sub-unit; or an end capsule compartment, an intermediate solid sub-unit and an end solid sub-unit.

9. A dosage form according to any preceding claim wherein adjacent sub-units are connected together by means of a weld,

10. A dosage form according to claim 9 wherein a weld is achieved by bringing sub-units into adjacent contact and applying localised heating or an ultrasonic horn.

11. A dosage form according to any preceding claim wherein adjacent sub-units have substantially planar regions of their surface which may be brought into contact.

12. A dosage form according to any one of claims 1 to 10 wherein adjacent sub-units have regions of their surface of complementary shapes, thereby facilitating connecting sub-units together.

13. A dosage form according to any preceding claim wherein adjacent sub-units are provided with respectively inter-connectable first and second connectable parts such that the first part on one sub-unit may connect with the second part on an adjacent sub-unit.

14. A dosage form according to claim 13 wherein the connectable parts on the sub-units are common so that the sub-units may be connected together in a wide range of combinations.

15. A dosage form according to claim 13 or 14 wherein the respective first and second connectable parts are respectively interlocking female socket parts and corresponding male parts which fit into the female socket.

16. A dosage form according to claim 15 wherein the male and female parts are common so that any male part on any solid sub-unit or capsule compartment may interconnect with any female part part on another solid sub-unit or capsule compartment.

17. A dosage form according to any of claims 13 to 16 comprising a linear disposition of three or more sub-units, in which the or each intermediate sub-unit(s) is provided with one or more connectable parts, which connect with one or more connectable parts on an adjacent intermediate sub-unit.

18. A dosage form according to any of claims 7 to 17 wherein the end sub-units are provided with one or more connectable parts which may connect with connectable parts on an adjacent intermediate sub-unit and/or with one or more connectable parts on another end sub-unit.

19. A dosage form according to any preceding claim wherein one or more of the sub-units are substantially cylindrical.

20. A dosage form according to claim 19 wherein capsule compartments are tub-shaped having a base closed by a base wall, and side walls extending upward from the base wall, and an upper open mouth.

21. A dosage form accoding to claim 20 wherein capsule compartments may connect together by the base of a first capsule compartment fitting into the open

mouth of an adjacent capsule compartment, so as to close the mouth of the adjacent capsule compartment, and such that the base wall of the first compartment physically separates the compartments.

22. A dosage form according to claim 20 or 21 wherein solid sub-units are shaped so as to fit as a plug into the open mouth of an adjacent capsule compartment.

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23. A dosage form according to any one of claims 20 to 22 wherein solid sub-units are shaped so as to fit adjacent to and connect with the outer surface of the base wall of a capsule compartment.

24. A dosage form according to claim 23 wherein the base of a tub-shaped capsule compartment is provided externally with a male or female part and the adjacent solid sub-unit may be provided externally with a corresponding interconnecting female or male part.

25. A dosage form according to any one of claims 3 to 19 wherein one or more capsule compartments are made closed and in this closed form connect with one or more adjacent sub-units.

26. A dosage form according to claim 25 wherein one or more of the capsule compartments are made in the form of two part compartment shells, each part compartment shell comprising a closed end and side walls and having a mouth opening opposite the closed end, which connect together with their mouth openings facing to form the capsule compartment, and one or both of the closed ends may connect with an adjacent sub-unit.

27. A dosage form according to any preceding claim wherein the wall of any capsule compartment present in the dosage form and the matrix of any solid sub-units comprises any pharmaceutically acceptable polymer selected from polyvinyl alcohol, natural polymers, polyethylene glycols, polyethylene oxides, mixtures of

PEGs and PEOs, hydroxypropylmethylcellulose, methylcellulose, hydroxyethylcellulose, hydroxyethyl methylcellulose, hydroxypropylcellulose, methacrylic acid copolymer, ammonium methacrylate copolymers, carboxymethylcellulose, povidone (polyvinyl pyrrolidone), polyglycolysed glycerides, carboxyvinyl polymers, polyoxyethylene-polyoxypropylene copolymers, amylose, cross-linked amylose and amylose-pectin combinations.

28. A dosage form according to any preceding claim wherein the sub-units differ in their drug content and/or drug content release characteristics.

29. A dosage form according to claim 28 wherein two or more sub-units each contain different drug substances, and/or different drug substance formulations.

30. A dosage form according to any preceding claim wherein one or more solid sub-units and/or capsule compartments are present which are substantially immediate release sub-units.

31. A dosage form according to any preceding claim wherein one or more solid sub-units and/or capsule compartments are present which are sustained-release sub-units.

32. A dosage form according to any preceding claim wherein one or more solid sub-units and/or capsule compartments are present which are pulsed-release sub-units releasing their drug content at a specific predetermined point in a patients gastro-intestinal system.

33. A dosage form according to any one of the preceding claims wherein one of the end sub-units is a substantially immediate-release compartment.

34. A sub-unit for use in the assembled dosage form according to any one of claims 1 to 33.

35. A moulding process wherein sub-units of the dosage form according to any one of claims 1 to 34 are made in respective mould cavities.

36. A mould or die suitable for use in the moulding process of claim 35.

Snap 2-pic 1

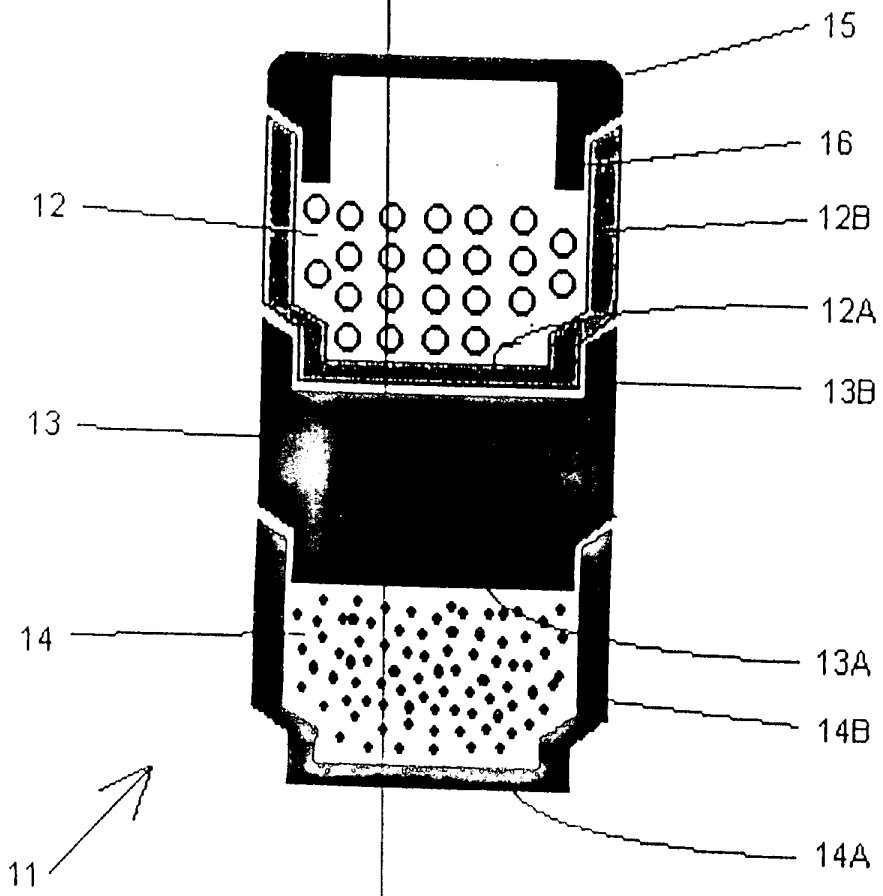

Fig. 1

Snap 2

Snap2-pic2

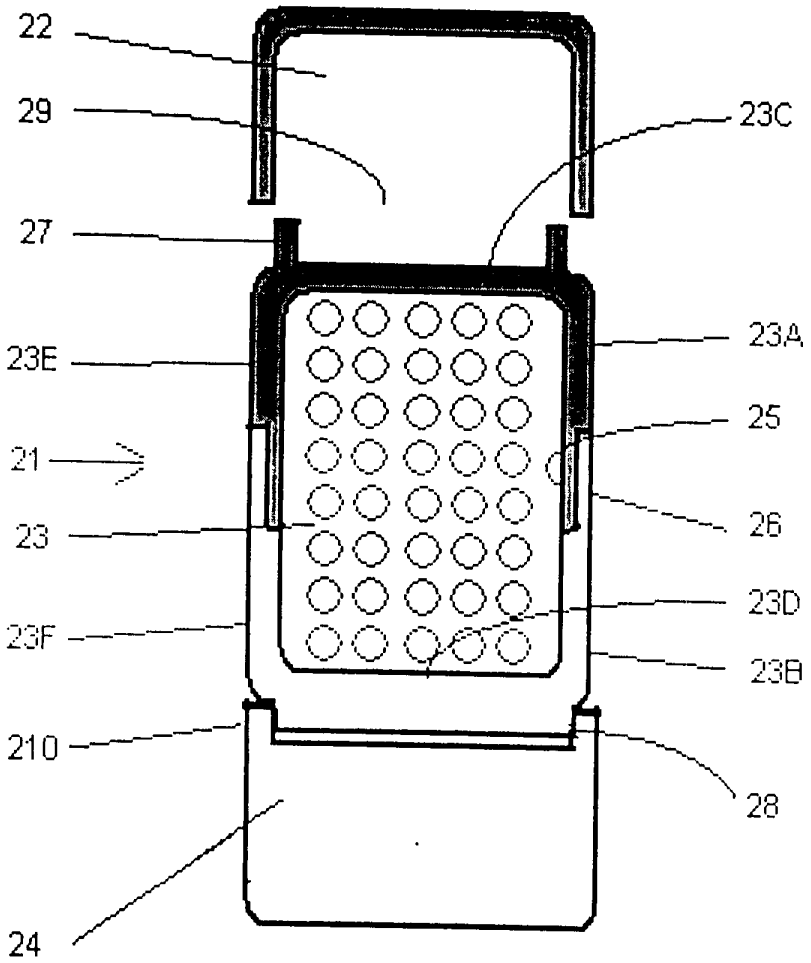

Fig. 2

Snap 2-pic3

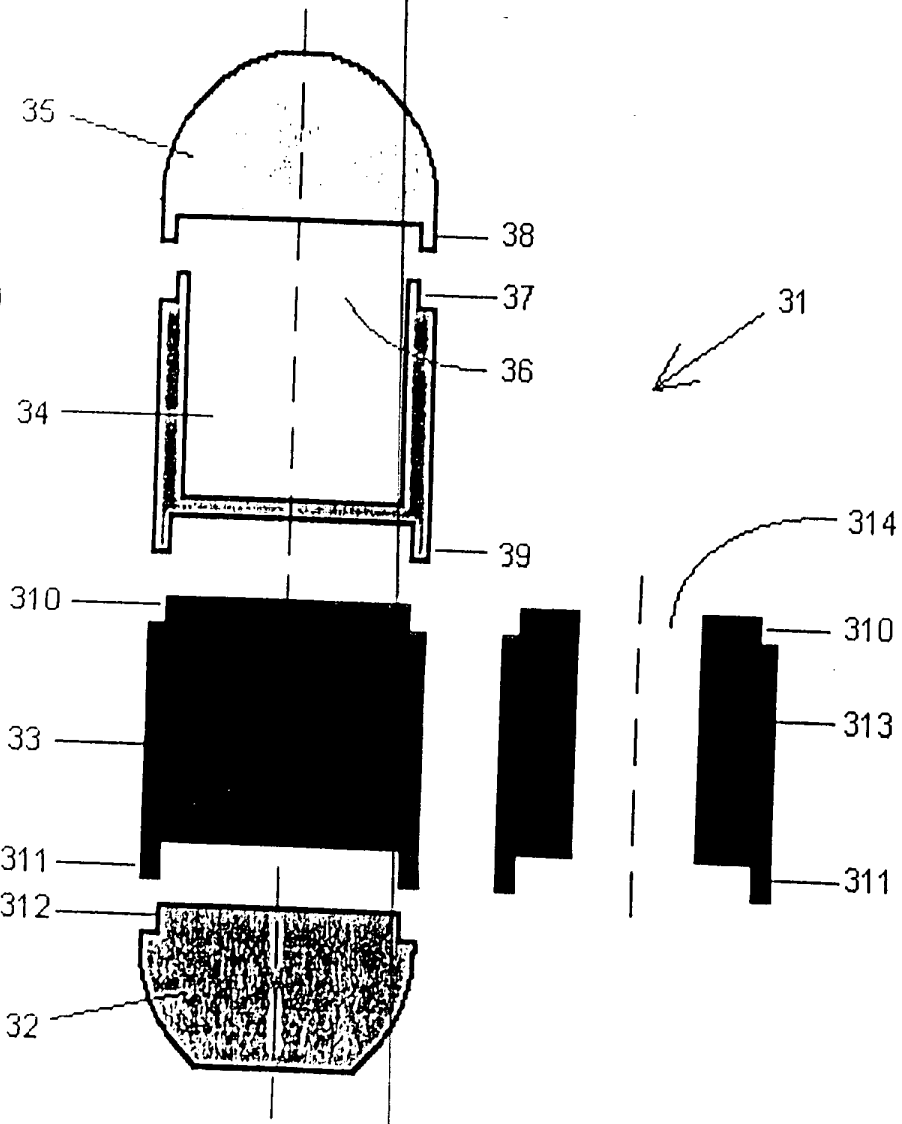

FIG 3